B. Prodrugs

A *prodrug* is a compound resulting from chemical modification of a biologically active compound that will liberate the active form in vivo by enzymatic or hydrolytic cleavage. The primary purpose in forming a prodrug is to modify the physicochemical properties of the drug, usually to alter the membrane permeability of the parent compound. This change in physicochemical properties of the drug influences the ultimate localization of the drug. There are various reasons for formulating a prodrug system. If the parent compound is insoluble, this can be modified [62]. If it is easily degraded, modification can protect the parent compound from enzymatic or hydrolytic attack. Modifications can also reduce side effects, such as GI irritation [63]. Several drugs are now marketed in the form of a prodrug; for example, sulindac, a nonsteroidal anti-inflammatory agent, and numerous angiotension-converting enzyme (ACE) inhibitors. The necessary conversion of prodrug to parent can occur by a variety of reactions, the most common being hydrolytic cleavage [64]. The prodrug ester forms of a hydroxyl or carboxyl group of the parent compound can be readily cleaved by blood esterase. Other activation processes may include biochemical reduction or oxidation. However the conversion occurs, to achieve sustained drug action, the rate of conversion from prodrug to active compound should not be too high [65]. Site-specific, controlled delivery is achieved by the antiviral prodrug acyclovir, being converted to active form by a virus-specific enzyme [66]. Sustained release of steroid prodrugs, especially progestagens and progestagen–estrogen combinations, have seen a substantial amount of clinical experience, both as a means of birth control and as symptomatic menopausal treatment [67].

The concept of the double prodrug (proprodrugs), may allow more controlled delivery of various prodrug compounds [68]. For example, if a prodrug that shows site-specific activation, but has poor transport properties or stability problems, it could be converted to a proprodrug that transported better or is more stable (Fig. 12). Prodrug systems have been taken even further by including as prodrugs, polymer prodrugs, in which a drug is covalently linked to a polymer backbone. This type of system could encompass a staggering number of possibilities. Encouraging results have been shown with mitomycin [69,70], for example.

The most serious disadvantage to the prodrug approach to controlled–sustained delivery is that extensive development must be undertaken to find the correct chemical modification for a specific drug. Additionally, once a prodrug is formed, it is a new drug entity and, therefore, requires extensive and costly studies to determine safety and efficacy.

C. Nanoparticles

Nanoparticles are solid colloidal particles ranging in size from 10 to 1000 nm. They can be used as drug carriers, with the drug encapsulated, dissolved, adsorbed, or covalently attached

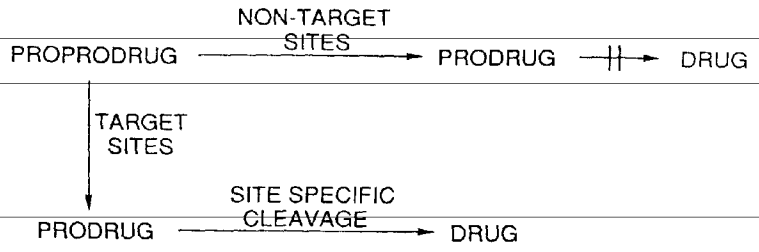

Fig. 12 Illustration of prodrug and proprodrug concept.